FRUITS, VEGETABLES AND LUNG CANCER: A POOLED ANALYSIS OF COHORT STUDIES

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Inverse associations between fruit and vegetable consumption and lung cancer risk have been consistently reported. However, identifying the specific fruits and vegetables associated with lung cancer is difficult because the food groups and foods evaluated have varied across studies. We analyzed fruit and vegetable groups using standardized exposure and covariate definitions in 8 prospective studies. We combined study-specific relative risks (RRs) using a random effects model. In the pooled database, 3,206 incident lung cancer cases occurred among 430,281 women and men followed for up to 6–16 years across studies. Controlling for smoking habits and other lung cancer risk factors, a 16–23% reduction in lung cancer risk was observed for quintiles 2 through 5 *vs.* the lowest quintile of consumption for total fruits (RR = 0.77; 95% CI = 0.67–0.87 for quintile 5; *p*-value, test for trend < 0.001) and for total fruits and vegetables (RR = 0.79; 95% CI = 0.69–0.90; *p*-value, test for trend = 0.001). For the same comparison, the association was weaker for total vegetable consumption (RR = 0.88; 95% CI = 0.78–1.00; *p*-value, test for trend = 0.12). Associations were similar between never, past, and current smokers. These results suggest that elevated fruit and vegetable consumption is associated with a modest reduction in lung cancer risk, which is mostly attributable to fruit, not vegetable, intake. However, we cannot rule out the possibility that our results are due to residual confounding by smoking. The primary focus for reducing lung cancer incidence should continue to be smoking prevention and cessation.
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Lung cancer is the most common cancer in the world.[1] Although cigarette smoking is the primary cause of lung cancer,[2–4] other factors, such as diet, have been hypothesized to influence lung cancer risk. Observational studies, mainly using a case-control design, have consistently shown an inverse association between fruit and vegetable intake and lung cancer risk.[5–7] However, because fruits and vegetables are heterogeneous with respect to phytochemical content and culinary usage,[8–11] associations with lung cancer risk may differ between groups of fruits and vegetables. Evaluation of the published literature for specific groups of fruits and vegetables is difficult due to the considerable variation in the food groups reported. In addition, investigators may tend to report results that are statistically significant, leading to publication bias. Therefore, we evaluated associations between specific and overall fruit and vegetable intakes and the risk of lung cancer in the Pooling Project of Prospective Studies of Diet and Cancer (Pooling Project). Using the primary data from each of the cohort studies, we standardized definitions of fruit and vegetable categories and covariates across studies and evaluated associations by smoking status and histologic type.

MATERIAL AND METHODS

The Pooling Project has been described previously.[12] For the lung cancer analyses, we identified 8 prospective studies[13–19] that met the following predefined criteria: at least 50 incident lung cancer cases; assessment of usual diet; conduct of a validation study of the diet assessment method or a closely related instrument; and assessment of smoking habits (Table I). Because most studies included only one sex, studies including women and men were analyzed as 2 separate cohorts. The person-time experienced during follow-up of the Nurses' Health Study (NHS) was divided into 2 asymptotically uncorrelated segments (NHSa, NHSb) for analysis to take advantage of the more detailed dietary assessment completed 6 years after baseline. According to the theory of survival data analysis, blocks of person-time in different time periods are asymptotically uncorrelated, regardless of the extent to which they are derived from the same people.[20] So, pooling

TABLE I – CHARACTERISTICS OF THE PROSPECTIVE COHORT STUDIES INCLUDED IN THE POOLED ANALYSIS OF FRUIT AND VEGETABLE INTAKE AND LUNG CANCER

Study	Years of follow-up	Sex	Baseline cohort	% current smokers	Number of cases	Total fruits		Total vegetables	
						No. of items	Median intake[c] (10–90%) g/day	Number of items	Median intake[c] (10–90%) g/day
Adventist Health Study	1976–1982	W	17,990	2	20	7	354 (133–652)	6	162 (74–269)
		M	12,526	6	31	7	310 (104–604)	6	151 (63–251)
Alpha-Tocopherol Beta Carotene Cancer Prevention Study	1985–1996	M	6,771[a]	100	298	26	121 (28–299)	38	94 (36–198)
Canadian National Breast Screening Study	1980–1993	W	56,837	20	149	6	314 (110–578)	15	221 (101–438)
Health Professionals Follow-Up Study	1986–1996	M	44,350	9	244	15	300 (98–621)	28	293 (141–550)
Iowa Women's Health Study	1986–1996	W	33,828	15	433	15	339 (131–624)	31	195 (92–383)
Netherlands Cohort Study	1986–1992	W	62,412	20	131	12	207 (83–389)	25	164 (89–295)
		M	58,279	33	843	12	155 (47–331)	25	157 (85–276)
New York State Cohort	1980–1987	W	21,045	23	130	8	290 (87–539)	23	188 (72–363)
		M	27,936	21	392	8	258 (71–492)	23	186 (76–341)
Nurses' Health Study a	1980–1986	W	88,307	29	156	6	272 (73–560)	13	150 (68–292)
Nurses' Health Study b	1986–1996	W	68,307[b]	21	379	21	329 (116–642)	33	259 (129–470)
Total			430,281		3,206				

[a]Only the placebo group of the Alpha-Tocopherol Beta Carotene Cancer Prevention Study is included in this analysis.–[b]The participants in the baseline cohort for the Nurses' Health Study b are included in the Nurses' Health Study a and are not included in the total.–[c]For context, 1 medium orange weighs 121 g, 6 ounces of orange juice weighs 187 g, and 1/2 cup cooked carrots weights 78 g.

estimates from these 2 time periods is a statistically valid alternative to using a single time period.

Dietary assessment

Diet was measured at baseline in each study using a food frequency questionnaire designed for that particular study. The number of fruit and vegetable questions ranged from 9 in the Sweden Mammography Cohort to 54 in the NHSb. Food group intakes were calculated by adding the intake data for the specific foods included in that food group that were listed on the study's food frequency questionnaire. We examined associations with fruits and fruit juice (total fruits); vegetables and vegetable juice (total vegetables); and fruits, vegetables and juice (total fruits and vegetables). Potatoes and mature beans were not classified as vegetables because of their high starch and protein content, respectively.[21] Associations also were examined for specific fruits and vegetables for which intakes were assessed as separate food items in over half the studies. The food frequency questionnaires from some studies collapsed multiple foods on a single line (*e.g.*, apples and pears); thus, in some cases, the results for multiple foods are presented together.

Validation studies[22–29] have been conducted for the food frequency questionnaires used in each cohort study in the Pooling Project or a closely related instrument. For vitamin C intake, a nutrient concentrated in fruits and vegetables, Spearman correlation coefficients between intakes from the food frequency questionnaire and the reference method generally ranged from 0.4 to 0.7 across the studies. Of the studies included in these analyses, only the Netherlands Cohort Study[27] and Alpha Tocopherol Beta-Carotene Cancer Prevention Study[23] have evaluated the validity of total fruits (Spearman correlation coefficients = 0.60 and 0.69, respectively) and total vegetables (Spearman correlation coefficients = 0.38 and 0.58, respectively) as a group. In the Nurses' Health Study[30] and Health Professionals Follow-Up Study,[31] correlations for total fruits and total vegetables were not evaluated; however, the median correlations comparing intakes of individual fruits and vegetables estimated from the food frequency questionnaire with those from multiple dietary records were approximately 0.3.

Assessment of nondietary risk factors

Information on potential nondietary risk factors was collected at baseline in each study using self-administered questionnaires designed for that particular study. For smoking history, each study assessed whether individuals had ever smoked or were current smokers. Among smokers, the number of cigarettes smoked per day and the years smoked were assessed.

Identification of lung cancer outcomes

Each study ascertained incident lung cancers using follow-up questionnaires with subsequent medical record review[13,16,32] and/or linkage with a cancer registry.[14–16,18,19,32] In addition, some studies used mortality registries or death certificates.[13,18,19,32] We categorized lung cancers based on the International Classification of Diseases for Oncology morphology codes[33] or the histologic classification provided by the original study investigators.

Statistical analysis

For each data set, after applying the exclusion criteria used by that study, we excluded participants if they reported energy intakes greater or less than 3 standard deviations from the study-specific log$_e$-transformed mean energy intake of the baseline population, reported a history of cancer (except nonmelanoma skin cancer) at baseline or were missing information on smoking habits.

Each study was analyzed using the Cox proportional hazards model. The Canadian National Breast Screening Study and Netherlands Cohort Study were analyzed as case-cohort studies[34] using Epicure software.[35] The remaining studies were analyzed using SAS PROC PHREG.[36] Person-years of follow-up were calculated from the date of the baseline questionnaire until the date of lung cancer diagnosis, death or end of follow-up, whichever came first. Age at baseline and the year the baseline questionnaire was returned were included as stratification variables. The proportion of missing values for each covariate was $< 7\%$ in each study; in the multivariate analyses, an indicator variable for missing responses was created for covariates, if applicable. Two-sided 95% confidence intervals and *p*-values were calculated. We calculated summary relative risks using the random effects model.[37] The study-specific log$_e$ relative risks were weighted by the inverse of their variance. We tested for heterogeneity among studies using the Q-statistic.[37,38]

We analyzed associations of risk with total fruits, total vegetables and total fruits and vegetables according to quintiles of consumption. Study-specific quintiles were assigned based on the distributions in the subcohort in the case-cohort studies and in the baseline cohort for the remaining studies. We also analyzed associations for these groups using cutpoints based on identical absolute intakes across studies; the Adventist Health Study was excluded from these analyses because there were few cases in this study. To calculate the *p*-value for the test for trend across cate-

gories of intake, participants were assigned the median value of their category and this variable was entered as a continuous term in the regression model.

Using a metaregression model,[39] we tested for variation in relative risks by sex, the number of fruit and vegetable questions included on the food frequency questionnaire and smoking status. We also tested whether associations differed between adenocarcinomas, small cell carcinomas and squamous cell carcinomas using a 2 degree of freedom-squared Wald test statistic.[40] Collectively, these 3 histologic types represented at least 60% of the cases in each study.

RESULTS

In the 8 studies in this analysis, 3,206 lung cancer cases (1,398 women, 1,808 men) occurred among over 280,419 women and 149,862 men (Table I). There were 280 cases among never smokers, 1,004 among past smokers and 1,922 among current smokers. Fruit consumption was highest among never smokers and lowest among current smokers. For vegetables, intakes among never and past smokers generally were similar and exceeded intakes among current smokers (Table II).

In the age-adjusted analyses, lung cancer risk was reduced by 29–56% for comparisons of the highest *vs.* lowest quintile of total fruit, total vegetable and total fruit and vegetable intakes (Table III). Adjustment for education, body mass index, alcohol intake and energy intake did not materially change the relative risks (results not shown). The associations were substantially attenuated after additional adjustment for smoking status (multivariate 1, Table III). Further attenuation occurred when duration of smoking and the amount smoked were included in the model (mulitvariate 2, Table III). Similar associations were observed for quintiles 2 through 5 relative to quintile 1. For comparisons of the highest *vs.* lowest quintile of intake, the pooled multivariate relative risks were 0.77 (95% CI = 0.67–0.87) for total fruits (Fig. 1) and 0.88 (95% CI = 0.78–1.00) for total vegetables (Fig. 2). The test for heterogeneity among studies was not significant for total fruits, total vegetables or total fruits and vegetables, indicating that the differences in relative risks across the studies were compatible with random variation. No associations were significantly modified by sex, although associations tended to be stronger and statistically significant among men compared to women. There was no evidence of effect modification by the number of fruit and vegetable questions included on a study's food frequency questionnaire (*p*-value = 0.98 for total fruits, 0.44 for total vegetables, 0.74 for total fruits and vegetables). Similar patterns in relative risks were

observed when we excluded cases who died within 1 year of diagnosis (number of cases in analysis = 1,472; results not shown) and when we stratified the cases by age at diagnosis. For lung cancers identified in individuals younger than 65 years, the pooled multivariate relative risks (95% CI) comparing the highest *vs.* lowest quartile were 0.83 (0.69–1.00) for total fruits, 0.75 (0.63–0.89) for total vegetables and 0.74 (0.62–0.89) for total fruits and vegetables. For lung cancers identified in individuals 65 years and older, the corresponding relative risks were 0.72 (0.60–0.87) for total fruits, 1.09 (0.86–1.38) for total vegetables and 0.85 (0.70–1.03) for total fruits and vegetables. Results were similar after further adjustment for multivitamin use (results not shown). Simultaneous adjustment for total fruit and total vegetable intakes (results not shown) did not materially alter the results observed when each group was analyzed separately. Models that controlled for smoking using a 10-level variable accounting for smoking status, amount smoked and years smoked or that controlled for smoking pack-years each yielded relative risks for the dietary variables intermediate between those observed for the model adjusting for smoking status only (multivariate 1, Table III) and the model adjusting for smoking status, duration of smoking and amount smoked (multivariate 2, Table III). Results from models that included a squared term for duration of smoking in addition to smoking status, duration of smoking and amount smoked were unchanged from those presented for the multivariate 2 model in Table III.

When we categorized fruit and vegetable intakes into deciles, the pooled multivariate relative risks for the highest *vs.* lowest decile of intake were 0.68 (95% CI = 0.56–0.83) for total fruits, 0.89 (95% CI = 0.75–1.06) for total vegetables and 0.74 (95% CI = 0.62–0.89) for total fruits and vegetables. Similar relative risks were observed for the quintile and decile analyses after excluding cases diagnosed during the first 2 years of follow-up (results not shown).

When total fruit and total vegetable intakes were analyzed as categories defined using identical absolute intake cutpoints across studies, the pooled multivariate relative risks were 0.82 (95% CI = 0.68–0.98) for total fruits and 0.90 (95% CI = 0.71–1.12) for total vegetables for comparisons of intakes of ≥ 400 *vs.* < 100 g/day (Fig. 3). For total fruits and vegetables, the pooled multivariate relative risks for comparisons of intakes of ≥ 600 *vs.* < 200 g/day were 0.76 (95% CI = 0.63–0.91; *p*-value, test for between-study heterogeneity = 0.38; *p*-value, test for between-study heterogeneity due to sex = 0.10).

TABLE II – AGE-ADJUSTED MEAN FRUIT AND VEGETABLE INTAKES (g/DAY) BY SMOKING STATUS

Study	Never smokers			Past smokers			Current smokers		
	Number of participants	Mean intakes (g/day)		Number of participants	Mean intakes (g/day)		Number of participants	Mean intakes (g/day)	
		Total fruits	Total vegetables		Total fruits	Total vegetables		Total fruits	Total vegetables
Adventist Health Study (W)	15,214	385	170	2,442	356	165	334	285	153
Adventist Health Study (M)	7,764	359	161	4,020	325	154	742	220	132
Alpha Tocopherol Beta-Carotene Cancer Prevention Study[a]							6,771	149	109
Canadian National Breast Screening Study[b]	2,688	353	246	1,462	348	267	1,064	287	245
Health Professionals Follow-Up Study	21,274	368	330	18,922	334	330	4,140	265	301
Iowa Women's Health Study	22,399	388	226	6,456	361	233	4,969	298	210
Netherlands Cohort Study (W)[b]	941	239	181	309	219	184	311	201	178
Netherlands Cohort Study (M)[b]	202	211	170	753	187	175	478	154	169
New York State Cohort (W)	10,773	322	208	5,448	322	217	4,824	261	193
New York State Cohort (M)	8,458	304	205	13,666	279	205	5,812	223	182
Nurses' Health Study a	38,469	328	171	24,467	321	178	25,358	261	165
Nurses' Health Study b	30,166	388	285	23,820	368	298	14,309	307	268

[a]The Alpha Tocopherol Beta-Carotene Cancer Prevention Study only includes current smokers.–[b]Only data for the subcohort were used to calculate mean intakes.

TABLE III – POOLED RELATIVE RISKS (95% CONFIDENCE INTERVALS) OF LUNG CANCER FOR QUINTILES OF FRUIT AND VEGETABLE INTAKE

| | Quintile of intake | | | | | *p*-value, test for trend | *p*-value, test for between-study heterogeneity for quintile 5 | *p*-value, test for between-study heterogeneity due to sex for quintile 5 |
	1	2	3	4	5			
Total fruits								
Age-adjusted								
Women	1.00	0.57 (0.47–0.70)	0.46 (0.36–0.58)	0.47 (0.38–0.57)	0.44 (0.37–0.51)	< 0.001	0.45	
Men	1.00	0.69 (0.57–0.82)	0.57 (0.44–0.73)	0.56 (0.45–0.69)	0.43 (0.34–0.56)	< 0.001	0.10	
Total	1.00	0.63 (0.55–0.72)	0.51 (0.43–0.60)	0.51 (0.44–0.59)	0.44 (0.38–0.50)	< 0.001	0.26	0.89
Multivariate 1 [a,b]								
Women	1.00	0.74 (0.63–0.86)	0.68 (0.53–0.87)	0.74 (0.62–0.88)	0.70 (0.59–0.84)	< 0.001	0.77	
Men	1.00	0.77 (0.66–0.91)	0.69 (0.56–0.86)	0.72 (0.58–0.89)	0.62 (0.51–0.74)	< 0.001	0.39	
Total	1.00	0.75 (0.67–0.84)	0.69 (0.59–0.81)	0.73 (0.64–0.82)	0.66 (0.58–0.75)	< 0.001	0.68	0.33
Multivariate 2 [a,c]								
Women	1.00	0.82 (0.70–0.96)	0.79 (0.63–0.98)	0.86 (0.72–1.02)	0.83 (0.70–1.00)	0.07	0.80	
Men	1.00	0.82 (0.69–0.96)	0.77 (0.62–0.95)	0.81 (0.66–0.99)	0.70 (0.57–0.87)	0.003	0.29	
Total	1.00	0.82 (0.73–0.91)	0.78 (0.67–0.90)	0.83 (0.74–0.94)	0.77 (0.67–0.87)	< 0.001	0.56	0.20
Total vegetables								
Age-adjusted								
Women	1.00	0.82 (0.70–0.96)	0.69 (0.59–0.82)	0.73 (0.62–0.85)	0.75 (0.64–0.88)	0.001	0.68	
Men	1.00	0.88 (0.76–1.03)	0.79 (0.68–0.93)	0.76 (0.65–0.90)	0.67 (0.57–0.79)	< 0.001	0.85	
Total	1.00	0.85 (0.76–0.95)	0.74 (0.66–0.83)	0.75 (0.66–0.84)	0.71 (0.63–0.80)	< 0.001	0.86	0.36
Multivariate 1 [a,b]								
Women	1.00	0.87 (0.71–1.06)	0.79 (0.66–0.93)	0.83 (0.70–0.99)	0.87 (0.73–1.04)	0.17	0.73	
Men	1.00	0.94 (0.80–1.10)	0.86 (0.71–1.06)	0.84 (0.71–0.99)	0.76 (0.63–0.90)	0.01	0.70	
Total	1.00	0.92 (0.82–1.03)	0.82 (0.73–0.92)	0.84 (0.74–0.94)	0.81 (0.72–0.92)	0.004	0.79	0.27
Multivariate 2 [a,c]								
Women	1.00	0.90 (0.74–1.09)	0.82 (0.68–0.99)	0.90 (0.76–1.07)	0.93 (0.78–1.12)	0.59	0.71	
Men	1.00	0.96 (0.81–1.13)	0.92 (0.74–1.15)	0.90 (0.75–1.07)	0.83 (0.69–1.00)	0.08	0.58	
Total	1.00	0.94 (0.83–1.05)	0.87 (0.76–0.99)	0.90 (0.80–1.02)	0.88 (0.78–1.00)	0.12	0.76	0.36
Total fruits and vegetables								
Age-adjusted								
Women	1.00	0.63 (0.54–0.74)	0.59 (0.48–0.71)	0.50 (0.42–0.59)	0.48 (0.41–0.57)	< 0.001	0.57	
Men	1.00	0.64 (0.55–0.75)	0.60 (0.52–0.71)	0.55 (0.45–0.66)	0.48 (0.38–0.60)	< 0.001	0.17	
Total	1.00	0.64 (0.57–0.71)	0.59 (0.53–0.67)	0.52 (0.46–0.58)	0.48 (0.43–0.54)	< 0.001	0.42	0.88
Multivariate 1 [a,b]								
Women	1.00	0.80 (0.68–0.93)	0.81 (0.68–0.95)	0.74 (0.62–0.87)	0.71 (0.59–0.86)	< 0.001	0.95	
Men	1.00	0.72 (0.61–0.84)	0.70 (0.60–0.83)	0.67 (0.54–0.84)	0.64 (0.51–0.80)	0.003	0.26	
Total	1.00	0.76 (0.68–0.85)	0.75 (0.67–0.84)	0.70 (0.62–0.79)	0.67 (0.59–0.77)	< 0.001	0.74	0.39
Multivariate 2 [a,c]								
Women	1.00	0.87 (0.74–1.02)	0.92 (0.78–1.09)	0.86 (0.72–1.02)	0.85 (0.70–1.02)	0.07	0.97	
Men	1.00	0.76 (0.64–0.90)	0.78 (0.66–0.92)	0.76 (0.61–0.95)	0.74 (0.59–0.94)	0.04	0.22	
Total	1.00	0.81 (0.72–0.91)	0.84 (0.75–0.95)	0.80 (0.70–0.90)	0.79 (0.69–0.90)	0.001	0.70	0.30

[a]Adjusted for education (< high school, high school, > high school), body mass index (< 23, 23 to < 25, 25 to < 30, ≥ 30 kg/m^2), alcohol intake (0, > 0 to < 5, 5 to < 15, 15 to < 30, ≥ 30 g/day) and calories (continuous).–[b]Also adjusted for smoking status (never, past, current).–[c]Also adjusted for smoking status (never, past, current), smoking duration for past smokers (continuous), smoking duration for current smokers (continuous), amount smoked for current smokers (continuous).
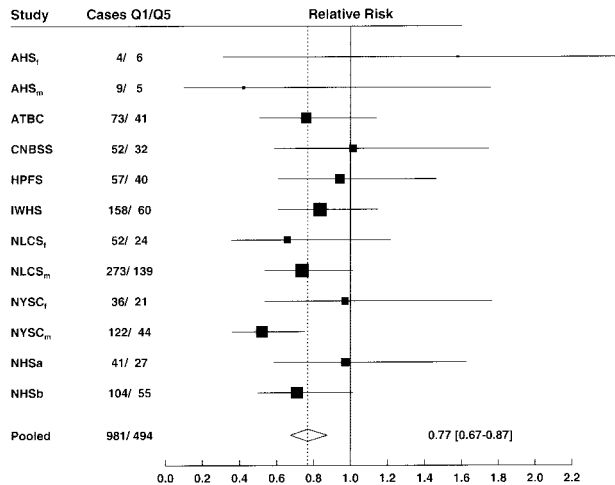
FIGURE 1 – Study-specific and pooled multivariate-adjusted relative risks of lung cancer and total fruit consumption, quintile 5 *vs.* quintile 1. The black squares and horizontal lines correspond to the study-specific relative risks and 95% confidence intervals for the comparison of quintile 5 to quintile 1 of total fruit consumption. The area of the black squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled relative risk and 95% confidence interval. AHS_f, female cohort of the Adventist Health Study; AHS_m, male cohort of the Adventist Health Study; ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; CNBSS, Canadian National Breast Screening Study; HPFS, Health Professionals Follow-Up Study; IWHS, Iowa Women's Health Study; $NLCS_f$, female cohort of the Netherlands Cohort Study; $NLCS_m$, male cohort of the Netherlands Cohort Study; $NYSC_f$, female cohort of the New York State Cohort; $NYSC_m$, male cohort of the New York State Cohort; NHSa, Nurses' Health Study a; NHSb, Nurses' Health Study b.
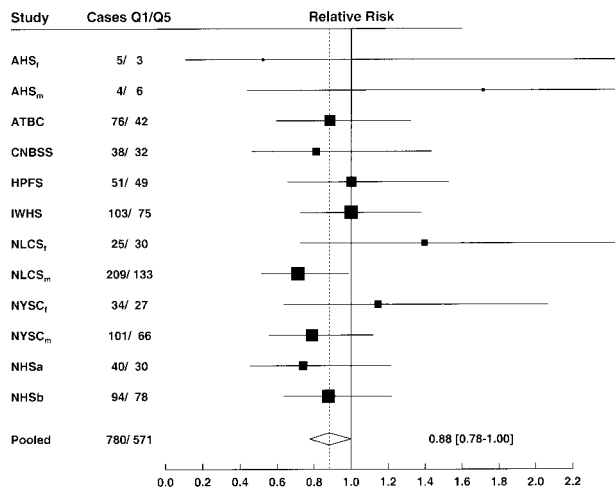
FIGURE 2 – Study-specific and pooled multivariate-adjusted relative risks of lung cancer and total vegetable consumption, quintile 5 *vs.* quintile 1. The black squares and horizontal lines correspond to the study-specific relative risks and 95% confidence intervals for the comparison of quintile 5 to 1 of total vegetable consumption. The area of the black squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled relative risk and 95% confidence interval. See legend to Figure 1 for abbreviations.

Specific fruits and vegetables

We observed inverse associations for apples and pears; oranges and tangerines; and orange and grapefruit juice (Table IV). After
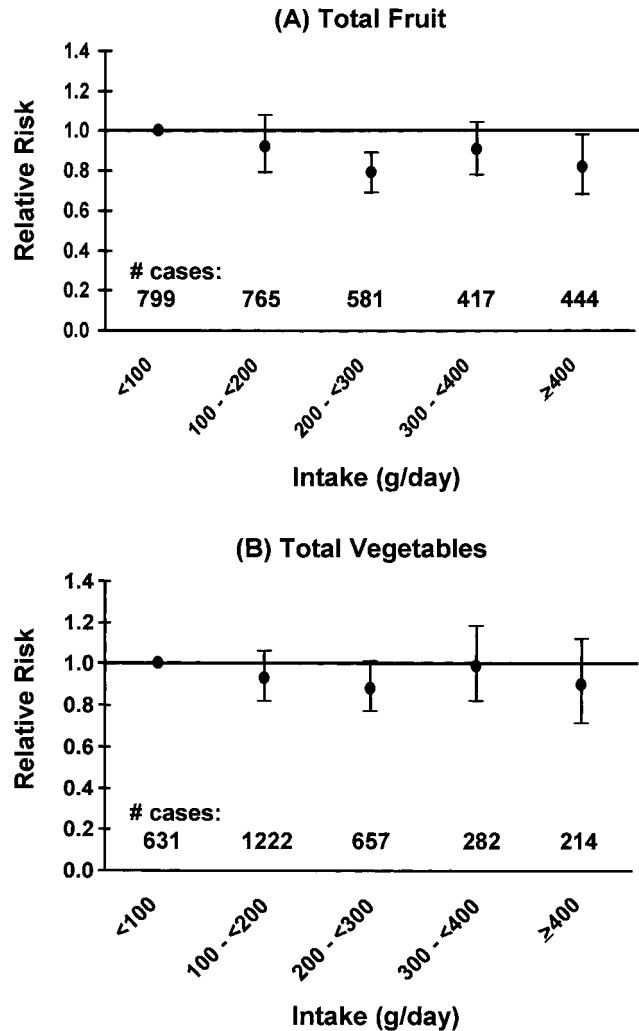
FIGURE 3 – Pooled multivariate relative risks and 95% confidence intervals for lung cancer by categories of intake. In the total vegetable analyses, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study did not include any cases with vegetable intakes exceeding 400 g/day.

further adjustment for total fruit consumption, only the association for oranges and tangerines remained statistically significant (results not shown). None of the 9 specific vegetables examined was associated with the risk of lung cancer. Green leafy vegetable consumption (*e.g.*, spinach, lettuce, mustard/collard greens, kale) was marginally significantly associated with lung cancer risk (pooled multivariate RR = 0.93; 95% CI = 0.81–1.07 comparing intakes of $\geq$ 1/2 serving/day *vs.* < 1 serving/week; *p*-value, test for trend = 0.07; *p*-value, test for between-study heterogeneity = 0.45).

Evaluation of heterogeneity

We analyzed whether associations of risk with total fruits, total vegetables and total fruits and vegetables differed by smoking status (Table V). For comparability across the smoking groups in these analyses, intakes were categorized into quartiles because the number of lung cancer cases among never smokers was limited. For total fruits, a nonsignificant 41% lower risk was observed among never smokers for comparisons of the highest *vs.* lowest quartile of consumption. Weaker associations were observed among current and past smokers but the differences between the 3 smoking strata were not statistically significant (*p*-value, test for

TABLE IV – POOLED MULTIVARIATE RELATIVE RISKS (95% CONFIDENCE INTERVALS) OF LUNG CANCER BY CATEGORY OF INTAKE OF SPECIFIC FRUITS AND VEGETABLES

	Serving size		0	> 0 to > 1 serving/week	1 serving/week to 1/2 serving/day (or ≥ 1 serving/week if highest category[a])	≥ 1/2 serving/day	p-value, test for trend	p-value, test for between-study heterogeneity for the highest category	p-value, test for between study heterogeneity due to sex for the highest category
Fruits									
Apples, pears[b]	1	Number	627	1,097	729	685			
		RR (95% CI)	1.00	0.89 (0.78–1.02)	0.81 (0.69–0.94)	0.80 (0.68–0.94)	0.03	0.23	0.41
Bananas[b]	1	Number	893	1,135	723	361			
		RR (95% CI)	1.00	0.97 (0.86–1.10)	0.90 (0.80–1.02)	1.04 (0.89–1.22)	0.61	0.74	0.32
Oranges, tangerines[b-d]	1	Number	750	789	721	410			
		RR (95% CI)	1.00	0.82 (0.66–1.02)	0.74 (0.62–0.89)	0.74 (0.58–0.95)	0.006	0.01	0.93
Orange and grapefruit juice[b,c]	6 oz	Number	1,118	544	360	817			
		RR (95% CI)	1.00	0.90 (0.79–1.02)	0.82 (0.71–0.95)	0.82 (0.71–0.94)	0.01	0.27	0.11
Vegetables									
Beans (string)[b,e]	1/2 cup	Number	376	1,169	1,085				
		RR (95% CI)	1.00	1.12 (0.94–1.33)	1.11 (0.87–1.43)		0.67	0.25	0.01
Broccoli[b,c,f]	1/2 cup	Number	575	1,188	409				
		RR (95% CI)	1.00	1.00 (0.85–1.18)	1.05 (0.89–1.24)		0.33	0.68	0.38
Cabbage[b,d,g]	1/2 cup	Number	405	1,381	1,062				
		RR (95% CI)	1.00	1.06 (0.92–1.22)	1.01 (0.88–1.17)		0.62	0.79	0.50
Carrots[b]	1 or 1/2 cup	Number	362	1,683	889	217			
		RR (95% CI)	1.00	0.86 (0.75–0.98)	0.88 (0.76–1.01)	0.91 (0.75–1.11)	0.65	0.61	0.96
Lettuce[b,e,g]	1 cup	Number	393	1,019	879	735			
		RR (95% CI)	1.00	0.93 (0.77–1.12)	0.83 (0.67–1.02)	0.90 (0.74–1.10)	0.07	0.79	0.63
Peas, lima beans[b,f]	1/2 cup	Number	282	925	966				
		RR (95% CI)	1.00	1.00 (0.87–1.15)	1.03 (0.89–1.18)		0.74	0.42	0.87
Tomatoes[b,g]	1	Number	372	1,014	1,120	488			
		RR (95% CI)	1.00	0.88 (0.75–1.03)	0.87 (0.74–1.02)	0.83 (0.67–1.03)	0.10	0.53	0.90
Mature beans or lentils[c]	1/2 cup	Number	989	1,570	308				
		RR (95% CI)	1.00	1.02 (0.90–1.15)	1.01 (0.85–1.19)		0.89	0.54	0.18

Adjusted for education (< high school graduate, high school graduate, > high school graduate), body mass index (< 23, 23 to < 25, 25 to < 30, ≥ 30 kg/m²), alcohol intake (0, > 0 to < 5, 5 to < 15, 15 to < 30, ≥ 30 g/day), calories (continuous), smoking status (never, past, current), smoking duration for past smokers (continuous), smoking duration for current smokers (continuous), amount smoked for current smokers (continuous).–[a]The ≥ 1 serving/week category was used if there were insufficient cases in the ≥ 1/2 serving/day category.–[b]The Adventist Health Study was excluded from this specific food analysis.–[c]The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was excluded from this specific food analysis.–[d]The Canadian National Breast Screening Study was excluded from this specific food analysis.–[e]The New York State Cohort was excluded from this specific food analysis.–[f]The Netherlands Cohort Study was excluded from this specific food analysis.–[g]The Nurses' Health Study a was excluded from this specific food analysis.

TABLE V – POOLED MULTIVARIATE RELATIVE RISKS (95% CONFIDENCE INTERVALS) OF LUNG CANCER FOR QUARTILES OF FRUIT AND VEGETABLE INTAKE BY SMOKING STATUS

		Quartile of intake				p-value, test for trend	p-value, test for between-study heterogeneity for quartile 4	p-value, test for between-study heterogeneity due to sex for quartile 4	p-value, test for between-study heterogeneity due to smoking status for quartile 4[d]
		1	2	3	4				
Total fruits									
Never smokers[a]	Number	69	57	70	63				
	RR (95% CI)	1.00	0.72 (0.49–1.06)	0.78 (0.47–1.29)	0.59 (0.34–1.04)	0.16	0.09	0.61	0.39
Past smokers[a,b]	Number	277	225	233	246				
	RR (95% CI)	1.00	0.85 (0.67–1.06)	0.85 (0.69–1.04)	0.85 (0.69–1.05)	0.43	0.49	0.49	
Current smokers[a,c]	Number	789	441	388	297				
	RR (95% CI)	1.00	0.83 (0.70–0.98)	0.85 (0.73–0.99)	0.82 (0.68–0.99)	0.02	0.23	0.13	
Total vegetables									
Never smokers[a]	Number	66	62	70	61				
	RR (95% CI)	1.00	0.94 (0.65–1.36)	1.02 (0.65–1.59)	0.90 (0.58–1.40)	0.75	0.35	0.09	0.72
Past smokers[a,b]	Number	256	235	246	244				
	RR (95% CI)	1.00	0.97 (0.77–1.22)	0.93 (0.75–1.15)	0.97 (0.76–1.24)	0.83	0.30	0.30	
Current smokers[a,c]	Number	620	454	437	404				
	RR (95% CI)	1.00	0.84 (0.73–0.96)	0.87 (0.74–1.02)	0.86 (0.74–1.00)	0.14	0.85	0.90	
Total fruits and vegetables									
Never smokers[a]	Number	70	56	73	60				
	RR (95% CI)	1.00	0.91 (0.58–1.42)	0.92 (0.56–1.53)	0.67 (0.38–1.19)	0.29	0.17	0.69	0.35
Past smokers[a,b]	Number	264	228	253	236				
	RR (95% CI)	1.00	0.87 (0.67–1.13)	0.95 (0.75–1.22)	0.85 (0.69–1.06)	0.29	0.84	0.61	
Current smokers[a,c]	Number	761	455	376	323				
	RR (95% CI)	1.00	0.83 (0.72–0.95)	0.79 (0.68–0.91)	0.84 (0.71–0.98)	0.03	0.58	0.61	

The Adventist Health Study was excluded from these analyses because this study had few cases in each of the smoking strata. Number of cases: 259 never smokers (183 women, 76 men), 981 past smokers (338 women, 643 men) 1,915 current smokers (857 women, 1,058 men).–[a]Adjusted for education (< high school graduate, high school graduate, > high school graduate), body mass index (< 23, 23 to < 25, 25 to < 30, ≥ 30 kg/m²), alcohol intake (0, > 0 to < 5, 5 to < 15, 15 to < 30, ≥ 30 g/day), calories (continuous).–[b]Also adjusted for smoking duration (continuous).–[c]Also adjusted for smoking duration (continuous) and amount smoked (continuous).–[d]Smoking status is categorized as never, past, and current smokers.

between-study heterogeneity due to smoking status = 0.39). Vegetable consumption was inversely associated with lung cancer risk among current smokers but not among never or past smokers (*p*-value, test for between-study heterogeneity due to smoking status = 0.72).

We also evaluated associations by histologic type of lung cancer (Table VI). Although there was a suggestion of a stronger inverse association for adenocarcinomas and squamous cell carcinomas compared to small cell carcinomas for total fruit and total fruit and vegetable intakes, the differences between the 3 histologic types were not statistically significant (*p*-value, test for common effects according to cell type for quartile 4 = 0.51 for total fruits and 0.57 for total fruits and vegetables). Total vegetable consumption was not associated with any of the 3 histologic types and the results were not significantly different across the 3 types (*p*-value, test for common effects according to cell type for quartile 4 = 0.63).

DISCUSSION

We observed 29–56% lower risks of lung cancer among men and women with higher intakes of total fruits, total vegetables and total fruits and vegetables in age-adjusted analyses. These reductions in risk were greatly attenuated when we controlled for smoking. When adjusted for smoking status, the number of cigarettes smoked and the number of years smoked, the relative risks for these groups for quintiles 2 through 5 compared to the lowest quintile of consumption were similar to each other and, in analyses of women and men combined, did not exceed a 24% reduction in lung cancer risk. Statistically significant inverse associations were observed for apples and pears; oranges and tangerines; and orange and grapefruit juice. Sex, smoking status and the number of fruit and vegetable questions on the food frequency questionnaire did not significantly modify the association between fruit and vegetable intakes and lung cancer risk. There was consistency in the results for total fruits, total vegetables and total fruits and vegetables from the multiple subgroup analyses compared with the overall results.

We analyzed the association between fruit and vegetable consumption and lung cancer risk using categories based on quantiles and on identical absolute intake cutpoints across studies. With the study-specific quantile approach, true differences in population intakes are not taken into account, potentially resulting in misclassification of exposure. However, misclassification could also occur in the analyses based on identical absolute intake cutpoints because reported intakes of fruits and vegetables have been shown to increase with the number of fruit and vegetable items on a questionnaire,[41] and there was a 5-fold variation in the number of fruit and vegetable items on the questionnaires among the studies in this analysis. Consequently, between-study differences in estimates of fruit and vegetable consumption may be due to differences in questionnaire design and/or in true intakes. Despite the different potential for misclassification between these 2 analytic approaches, the inverse association between fruit and vegetable consumption and lung cancer risk was not linear and of similar magnitude for both approaches.

A recent summary[6] of 17 case-control and 7 cohort studies concluded that the evidence is convincing that elevated intakes of fruits, vegetables, green vegetables and carrots reduce lung cancer risk. Several case-control studies have shown at least a 25% reduction in lung cancer risk for comparisons of the highest *vs.* lowest intake category for fruits[42–52] or vegetables.[45–49,51,53–63] Other case-control studies have shown weaker or nonsignificant associations.[44,50,52,54–58,60–71] Only a large case-control study among female nonsmokers reported a significant positive association for fruit consumption.[72] For carrots and green leafy vegetables, reductions in lung cancer risk of 40–60% generally have been observed in case-control studies for comparisons of the highest *vs.* lowest intakes.[42,43,45,47,49,51,52,55,59,62,63,65,73–81] However, in our analyses and among the cohort studies[78–80,82–86] that

TABLE VI – POOLED MULTIVARIATE RELATIVE RISKS (95% CONFIDENCE INTERVALS) OF LUNG CANCER FOR QUARTILES OF FRUIT AND VEGETABLE INTAKE BY CELL TYPE

| | Quartile of intake | | | | *p*-value, test for trend | *p*-value, test for heterogeneity for quartile 4 | *p*-value, test for between study heterogeneity due to for quartile 4 | *p*-value, test for common effects by cell type quartile 4 |
	1	2	3	4				
Total fruits								
Adenocarcinomas	1.00	0.84 (0.70–1.01)	0.84 (0.72–0.99)	0.84 (0.71–0.99)	0.10	0.48	0.72	
Small cell carcinomas	1.00	0.78 (0.61–1.00)	0.92 (0.69–1.24)	0.93 (0.71–1.23)	0.71	0.14	0.06	
Squamous cell carcinomas	1.00	0.70 (0.59–0.82)	0.75 (0.63–0.88)	0.75 (0.59–0.96)	0.01	0.17	0.12	0.51
Total vegetables								
Adenocarcinomas	1.00	0.88 (0.72–1.08)	0.97 (0.81–1.16)	0.91 (0.75–1.11)	0.53	0.25	0.75	
Small cell carcinomas	1.00	1.04 (0.82–1.31)	1.07 (0.81–1.40)	0.98 (0.77–1.26)	0.92	0.26	0.08	
Squamous cell carcinomas	1.00	0.86 (0.72–1.02)	0.86 (0.72–1.03)	0.94 (0.78–1.12)	0.84	0.53	0.08	0.63
Total fruits and vegetables								
Adenocarcinomas	1.00	0.81 (0.70–0.95)	0.88 (0.73–1.07)	0.80 (0.67–0.94)	0.02	0.73	0.55	
Small cell carcinomas	1.00	0.88 (0.73–1.05)	0.84 (0.69–1.03)	0.90 (0.73–1.11)	0.52	0.42	0.16	
Squamous cell carcinomas	1.00	0.71 (0.59–0.86)	0.81 (0.67–0.98)	0.76 (0.63–0.91)	0.01	0.50	0.19	0.57

Adjusted for education (< high school graduate, high school graduate, > high school graduate), body mass index (< 23, 23 to < 25, 25 to <30, ≥ 30 kg/m²), alcohol intake (0, > 0 to < 5, 5 to < 15, 15 to < 30, ≥ 30 g/day), calories (continuous), smoking status (never, past, current), smoking duration for past smokers (continuous), smoking duration for current smokers (continuous) and amount smoked for current smokers (continuous). The Adventist Health Study was excluded from these analyses because this study had few cases of each cell type. Number of cases: 956 adenocarcinomas (581 women, 375 men), 538 small cell carcinomas (256 women, 282 men), 901 squamous cell carcinomas (242 women, 659 men).

did not meet the criteria for inclusion in our study, weaker, and mostly nonsignificant, associations were observed for total vegetable, carrot and green leafy vegetable consumption. As in the case-control studies, an inverse association for total fruits was observed in our analyses, although nonsignificant associations have been observed in most,[78,79,82,86,87] but not all,[80,83] of the cohort studies not included in our analyses. We observed a nonlinear association for total fruits and vegetables and the risk of lung cancer that was increased only among those with the lowest intakes. These results suggest that even supplementation with the potentially biologically active compounds would have little effect in most persons, thus leading to a negative trial, as has been observed in some,[88,89] but not all,[90,91] clinical trials of beta-carotene supplementation.

Because smoking is strongly associated with lung cancer risk[2–4] and smokers eat fewer fruits and vegetables compared to never smokers,[92–97] differences in results across previous studies may be due in part to how smoking habits were controlled for in the multivariate models. Several studies have adjusted for smoking status only,[46,55,82] which in our analyses was associated with incomplete control of confounding by smoking compared to models that also adjusted for smoking duration and dose. Differences in the degree of residual confounding by unmeasured smoking habits also may impact the strength of the associations observed.

For example, we were unable to control for smoking inhalation patterns, the type of cigarettes smoked, pipe and cigar smoking and environmental tobacco smoke because most cohorts did not collect this information. If these variables confound the association between fruit and vegetable consumption and lung cancer risk, then our results are likely to be overestimates of the true association.[98,99] Arguing against residual confounding as the only explanation for the modest inverse association we observed for fruit consumption is the inverse association observed among never smokers.

In conclusion, we observed a modest nonlinear inverse association between fruit consumption and lung cancer risk with the highest risk limited to the lowest quintile of consumption. Little association was seen with vegetable intake. Because smoking is a strong risk factor for lung cancer[2–4] and because for the studies in this analysis, current smokers had lower total fruit and, to a lesser degree, total vegetable intakes compared to never smokers, we cannot rule out the possibility that our results are due to residual confounding by smoking. However, even if no residual confounding is present, the modest inverse association observed for fruit intake, and the absence of a reduction with vegetable intake, reinforces the public health message that the primary focus for reducing lung cancer incidence and mortality should be on smoking prevention and cessation.

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